ANTI-RABIC PROCEDURE IN PALESTINE WITH SPECIAL REFERENCE TO DECENTRALIZATION OF TREATMENT

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I. INTRODUCTION

Rabies has been known to be endemic in Palestine for very many years. The country, in virtue of its geographical position, is one peculiarly liable to the disease in that it is bounded on three sides by countries in which rabies is prevalent while its general configuration favours the continued existence of the common ' carriers ' of the disease—the jackal and the pariah dog.

In the decade immediately prior to 1923 in Palestine, the most convenient course open to persons bitten by animals suspected of rabies was to proceed to Jerusalem to attend for treatment at a private institute where Pasteur's original dried cord method was practised.

On the establishment of railway communications between Palestine and Egypt in 1918, however, the Army Authorities made the decision that all military personnel affected should be sent to the Anti-Rabic Institute in Cairo.

This somewhat unsatisfactory state of affairs continued until it became increasingly apparent that the necessity for the provision in Palestine itself of a mode of treatment, recognized as adequate both by Military and Civil Authorities alike, was absolute, if numbers of lives were not to be sacrificed every year. Such loss of life was ascribed to two causes : to lack of proper facilities for treatment in this country, and to ineffective treatment in Cairo consequent upon the lateness of arrival of the patients.

Early in 1923 the serious attention of the Department of Health was given to coping with the situation ; there was no doubt that persons in ever-increasing numbers were being bitten by rabid dogs and jackals all over Palestine ; the result was that an undertaking to supply an anti-rabic vaccine of undoubted reputation and of proved reliability,—one able to fulfil all army and civilian requirements—was given by the Laboratory Section of the Department.

Table I shows the number of untreated cases reported on as having died in hospitals during 1922 from Hydrophobia, and well illustrates the gravity of the situation at that time.

Table I.

No. of cases	Sex	Age	Wounds (all inflicted through naked skin and not cauterized)			Biting animal	In days	
			No.	Location	Gravity		Period of incubation of hydrophobia	Duration of symptoms
1	M	13	1	Outer surface lower leg	Slight	Dog	38	4
2	M	13	1	Finger	Slight	Dog	22	2
3	M	78	3	Dorsum of hand	Severe	Dog	44	4
4	M	47	3	Eyebrow, Nose, Upper Lip	Severe	Jackal	16	3
5	M	22	2	Hand	Slight	Dog	30	3
6	M	12	2	Ala and tip of nose	Medium	Dog	17	1
7	M	8	1	Tip of nose	Medium	Dog	44	2
8	M	45	2	Nose	Medium	Jackal	32	4

Additional considerations, however, emphasised the necessity for the undertaking, not the least amongst which was the fact that all expenses in connection with indigent patients presenting

themselves for treatment at the private institute in Jerusalem had to be defrayed by the Government at very considerable cost, while again, the Military Authorities were involved in much inconvenience and expenditure by having to send all bitten soldiers to Egypt.

It will be appreciated, therefore, that the Department's decision was based on strictly utilitarian and economic grounds.

II. SELECTION OF VACCINE

As the result of a lengthy and comprehensive survey of the various recognized modes of anti-rabic treatment, we finally resolved that the vaccine most suitable for Palestine was undoubtedly that originally introduced by Fermi of Sassari, modified by Semple, and elaborated by Harvey and McKendrick at the Central Institute, Kasauli.

The valuable reports issued by the Kasauli Institute, along with the published memoirs of Semple, on the one hand, and the close study, on the other, of the economic conditions of Palestine determined our selection.

The relative values of the three chief methods of treatment—all of which had received fair and full trial at Kasauli—are clearly enunciated by Harvey and Acton in their critical ' Examination into the degree of efficacy of anti-rabic treatment,' while the reasons which led up to the final adoption by that Institute of a carbolized vaccine in preference to the living viruses of Pasteur and Hoegyes are stated in convincing fashion.

After the inception of the Institute in 1900 the dried cord method of Pasteur was employed for seven years. While, admittedly, this treatment was highly successful, yet the occurrence, though rare, of ' accidents paralytiques ' both during and after treatment could not be regarded otherwise than with disfavour. The possibility, however remote, of such accidents—believed by Harvey and McKendrick to be probably of an anaphylactic nature and due to the unavoidable introduction by this method of an excess of nerve protein during the course of injections—was responsible for a change being made to the dilution method of Hoegyes in 1907. This alteration in policy was in every way justified and the results of its adoption afforded striking confirmation of the theory advanced

by Harvey and McKendrick, for with the use of a comparatively small amount of foreign nerve protein coincided the complete cessation of cases of paralysis.

A further change of policy, however, took place in 1912 when, as a result of brilliant researches by Fermi, Semple and others, it was conclusively proved that the employment of a dead vaccine afforded a protection at least equal to that given by the living viruses of the previous methods.

Since that time the accumulated evidence of twelve years' experience has upheld beyond all question the opinion first put forward by Fermi as to the value of treatment by a carbolized vaccine.

Again, the stimulating example set by Col. Hamerton who, faced with an exceedingly difficult problem in Irak, most successfully coped with the situation there, proved a great encouragement to us, and so it was with every hope of similar success in Palestine that we established in Jerusalem, on May 1st, 1923, the Central Anti-Rabic Institute. In order, however, that the ' greatest good of the greatest number ' of inhabitants likely to be at risk might be served, ten subsidiary treatment centres in the districts, supplied with the vaccine prepared at the Central Institute, were opened on the same day.

III. PROCEDURE

It will be immediately obvious that if decentralization is to be successful, medical officers in charge of subsidiary centres must be completely conversant with all matters relating to anti-rabic procedure.

Each officer appointed to carry out such work here reports first to the Central Institute where he undergoes a full course of instruction.

During this course he has to give evidence that he has familiarized himself with the various considerations governing the policy adopted, with the whole subject of rabies and its prevention, and with every detail of procedure touching on the preparation, distribution, storage, and administration of the vaccine.

To ensure that each centre is conducted in strict accordance with instructions laid down, one or other of us carries out routine inspections.

A. General Considerations.

(1) *Was the biting animal rabid ?*

An animal should be considered rabid

(*a*) if it dies from an undiagnosed disease
(*b*) if it has been killed.
(*c*) if it has disappeared

} within ten days of its biting the patient.

(*d*) if it shows marked alteration in behaviour ; if, for example, it makes unprovoked assault on human beings or other animals, especially if such results in many persons or animals being bitten.

(*e*) if a jackal makes an unprovoked attack on a human being.

(2) *Has the patient been exposed to the risk of infection ?*

(*a*) A person cannot be infected by (the saliva of) an animal except when that animal is actually suffering from rabies and during the ten days immediately prior to that animal's developing symptoms (two to five days before the appearance of symptoms, Roux and Nocard, Nicholas).

(*b*) The contagion, no matter what its virulence or concentration, cannot penetrate uninjured skin or mucous membrane.

In this connection, wounds which have been granulating twenty-four hours or more are considered impervious to the virus.

A very definite risk of infection is run when blood or serum oozes from cut or abrasion.

B. Procedure to be followed.

(1) *In respect of the biting animal.*

(*a*) On no account should the animal be destroyed (there are, of course, necessary exceptions to this dictum). It should be kept under observation in close confinement, when it will, if infected and infective, have developed symptoms within ten days.

If, on the other hand, the animal remains healthy at the end of ten days, it can be regarded as having been free from the possibility of causing infection at the time of biting.

(*b*) If the animal dies during the period of observation (ten days) without showing the classical signs of rabies, it should, nevertheless, be considered as having been rabid in so far as the treatment of bitten persons is concerned.

(2) *In respect of the bitten person.*

(*a*) After giving suitable local treatment to the wound (*vide* below), one must pronounce upon the biting animal. If the animal appears to be normal it should ordinarily be kept under observation for ten days, at the end of which period, if it still shows no signs of disease, it can be considered to have been non-infective and the bitten person therefore free from risk. But treatment should be begun immediately (and to this there must be no exception made), in the following circumstances :—

(*a*) When the animal develops symptoms of ill-health, dies, is killed, or escapes, during its ten days' observation period.

(*b*) When the patient has been bitten on the face, on the hand, or very severely (even through clothing) in other parts of the body.

(*c*) If the patient has been bitten by an unknown animal in the dark or while asleep in the fields (common incident enough during the summer among the *Fellaheen*).

It is, however, of first importance to note that when an animal dies during its observation period, vaccine treatment must be begun at once, and on no account whatsoever should the result of the laboratory examination of the dead animal's brain be awaited. Apart from the loss of valuable time incurred by such a wait, it must be remembered that failure to find Negri-bodies by the microscopist does not always signify that the animal was free from rabies.

(3) *In respect of the bitten animal.*

See Appendix II, paragraphs 5 and 6.

C. Diagnosis of Canine Rabies.

(1) *Clinical.*

There exists at present no better description than that given by Mohler and Eichorn in their translation of Hutyra and Marek's textbook on 'Spezielle Pathologie und Therapie der Haustiere,' published by Ballière, Tindall and Cox, and to this the reader is referred.

(2) *Laboratory.*

The brain of a dog or other animal which has died of suspected rabies or which has been shot or otherwise killed as a result of its

having bitten persons or other animals should be extracted and forwarded to the Central Institute (here part of the Central Laboratories). A simple method of extraction is to saw the head sagittally and remove the two halves of the brain intact.

When the brain has to be sent from a distance for laboratory examination, the two halves, so extracted, are placed in a wide-mouthed can and packed about with well-powdered salt. The salt must completely fill the receptacle. The lid is now to be replaced and soldered by a tinsmith prior to despatch.

We advocate this procedure of forwarding in salt in preference to that usually recommended, viz. : in separate tins containing glycerine and alcohol respectively, because the brain thus arriving in a fresh state allows of full examination.

The brain is now freed from salt by washing in sterile normal saline solution.

Laboratory investigation consists of the search for Negri-bodies and of the performance of the biological test by rabbit inoculation.

For the detection of Negri-bodies, preliminary smears from the hippocampus major or cerebellum are made and coloured with Giemsa's stain. The results are controlled by examination of sections of these parts of the brain fixed in Zenker's fluid and coloured with haematoxylin-fuchsin or Mann's stain. With the latter we have found difficulty in obtaining uniformity of results, but with haematoxylin-fuchsin we have been very successful in accordance with the following procedure :—

(*a*) Stain with haematoxylin for seven to ten minutes.

(*b*) Blue well in tap water.

(*c*) Counterstain with acid fuchsin for three minutes.

(*d*) Differentiate in tap water.

(*e*) Pass rapidly through alcohol, clarify with oil of cloves, and mount in balsam.

In regard to the Biological Test : it is performed by injecting an anaesthetized rabbit sub-durally with 0.2 c.c. of a 1 per cent. emulsion previously prepared from the medulla of a suspected animal.

The emulsion is made by rubbing-up in sterile normal saline solution a small piece of the medulla and thereafter filtering the suspension through gauze. It is then introduced sub-durally by

means of a hypodermic syringe (the needle of which is bent at a right-angle) into an opening made by a small (Eyre's intracranial) trephine in one of the parietal bones of the rabbit. It need hardly be pointed out that the strictest aseptic precautions must be observed throughout the operation. After a variable length of time in positive tests symptoms of paresis occur, and death takes place usually in from fifteen to twenty-five days.

D. Treatment.

When it has been decided that a patient requires treatment certain curative methods are employed.

(1) *Local treatment.*

Every endeavour must be made to get rid of as much of the virus deposited in the wound as possible and that without delay. Such common expedients as ligaturing, when possible, the affected part, encouraging bleeding, and freely opening up and thoroughly cleansing the wound are to be resorted to.

Cauterization of every part of the wound must now be performed with such caustics as pure carbolic or fuming nitric acid. Here we employ fuming nitric acid and consider it likely to be effective only if applied within half-an-hour of the time of biting. (Adherence to this time limit enables us to state that in our series of cases, of 1,920 persons treated, only 40 were efficiently cauterized.)

(2) *General treatment.*

The patient must, during treatment and for ten days thereafter, follow a quiet well-ordered existence. Chill, fatigue, and excitement must be avoided, while alcohol should be especially restricted.

(3) *Specific treatment* (vaccine treatment).

E. The Vaccine.

(1) *Nature and Preparation.*

The vaccine prepared by the Central Institute consists of a 2 per cent. suspension of the brain of a rabbit killed with fixed virus, in a solution of 1 per cent. phenol in distilled water.

Before being bottled and issued to the ten treatment centres, however, it is diluted with an equal quantity of normal saline

solution. Rabbits of about 1,400 grammes are inoculated sub-durally with fixed virus emulsion, and this operation is performed only on such numbers of rabbits as will presumably supply all demands for vaccine and will keep the ' strain ' going.

Attention to the technique of the trephining and inoculating operations results in a minimal number of rabbits being required, and the practically 100 per cent. success obtained here is due to the operators' observing various essentials :

(*a*) Absolute asepsis throughout.

(*b*) Rapidity in carrying out the trephine portion of the operation.

(*c*) Slowness in injecting the emulsion of fixed virus along the needle, held parallel to the dura.

(*d*) Covering the trephine opening with a pad of sterile cotton wool and maintaining slight pressure during the process of inoculation and during the slow drawing-out of the needle on completion of the operation. This procedure precludes regurgitation of the virus emulsion.

(*e*) Care in the choice of the fixed virus used for passage.

The virus in use here was originally obtained from Cairo and produces symptoms usually on the fifth, though occasionally on the sixth day after sub-dural inoculation. Whereas, for the production of vaccine, the brain of any animal showing symptoms on the fifth or sixth day is used, here ' passage virus ' is invariably selected from the brains of those rabbits that have developed symptoms on the fifth day.

This we find most important in keeping up the fixity of the virus and in obtaining uniform results of virulence.

On the eighth or ninth day, then, after inoculation, the rabbits, now moribund, are killed by chloroform, dipped in a weak solution of cresol, and dissected.

The brain, after naked-eye inspection and after cultures have been taken from it to ensure sterility, is ' extracted ' and weighed in an accurate balance. Brains showing excessive haemorrhage or other abnormality are discarded. The brain is now pounded in a sterile mortar and during this process the carbolic solution is added little by little. On an average this operation should take from fifteen to twenty minutes to complete, and when the brain has been well-emulsified into a thick sticky paste, the remainder of the

carbolic solution is slowly mixed in, until a suspension of 1 in 50 of brain substance has been obtained.

We now have a 2 per cent. brain emulsion in a 1 per cent. carbolic solution and this is filtered through two la ers of gauze to get rid of the connective and vascular tissues, and then placed in an incubator at 37° C. for twenty-four hours.

Although all workers whose methods we have studied use a carbolic solution made up with normal saline, we, after repeated observation, have preferred to employ distilled water, as this we find gives a better suspension, while precipitation of the brain matter does not occur so readily as with saline.

After the emulsion has been in the incubator for twenty-four hours, it is taken out and mixed with an equal volume of normal saline so that the vaccine now consists of a 1 per cent. brain emulsion in 0.5 per cent. carbolic solution. After passing aerobic and anaerobic cultivation tests, the vaccine is run into sterile bottles of 30 c.c. capacity in which it is distributed. Of this vaccine each person, irrespective of age, sex, or severity of bite, receives intracutaneously 5 c.c. daily, 2.5 c.c. on each side of the abdomen.

In the first year of work here, we diluted the above suspension further with an equal quantity of normal saline just before its administration, thus following the exact procedure (apart from the substitution of distilled water) described by Harvey and McKendrick and Col. Hamerton, and giving a 0.5 per cent. suspension of brain substance in 0.25 per cent. carbolic solution. In our second year, for considerations elsewhere discussed, it was decided to inject directly, without previous dilution, a 1 per cent. emulsion—and this has been in practice here since May, 1924.

(2) *Distribution, and instructions for use.*

Before despatch from the Central Institute the vaccine bottles are properly capped, paraffined, and labelled. On each label is given the following information : nature of the contents of the bottle ; the dosage ; the mode of administration ; and directions relating to storage. In addition to this, by means of a rubber stamp are affixed further particulars :—viz., the serial number of the vaccine, the date of manufacture, and the date on which the vaccine bottle—irrespective as to whether its contents have been used or

not—is to be returned as 'out of date' to the Central Institute. This date of return is invariably three months after the date of manufacture shown on the label of each bottle.

The medical officers in charge of the various treatment centres make known their requirements fortnightly, and these indents, when met, maintain the stock held by each centre at a constant level.

The vaccine is administered in accordance with the printed instructions wrapped round each bottle :—

(*a*) Sterilize 5 c.c. Record syringe.

(*b*) Shake the bottle well.

(*c*) Withdraw 5 c.c. of vaccine by pushing the needle of the syringe through the rubber cap (previously sterilized by dipping in alcohol).

(*d*) Inject 2.5 c.c. of the vaccine on one side of the abdomen and 2.5 c.c. on the other, by inserting the point of the needle at an acute angle between the superficial and deep layers of the skin (intracutaneously).

(*e*) The complete course of treatment consists of fourteen such injections of 5 c.c. on successive days.

(*f*) The same dose is given to children as to adults, and bites of all severities are treated alike.

F. Advantages of adopting this Method of Treatment.

(1) The employment of this carbolized anti-rabic vaccine precludes the possibility of its producing *per se* the disease its object is to prevent.

Cases recorded in literature show that the injection of living or merely somewhat attenuated virus is not entirely free from danger. Babes in this connection states : 'It is very probable that fixed virus in certain cases can produce hydrophobia after subcutaneous injections. The employment of this virus, therefore, must be prohibited in the treatment of human subjects unless the organism has been first prepared with a virus sufficiently attenuated.'

Surprising, indeed, is the number of persons requiring assurance that treatment itself involves no risk, and here one is frequently asked whether, should events prove that treatment was unnecessary, any harm can possibly ensue from the administration of vaccine.

With the use of carbolized vaccine, we are fortunately able to reassure patients completely in these respects.

(2) Its use is not followed by any harmful effects.

Occasionally local hyper-reaction occurs, due to individual idiosyncrasy. Here there has been no sign of abscess formation although over 60,000 intracutaneous inoculations have been made. Further, the vaccine contains the smallest amount of nervous tissue commensurate with efficient treatment, and thereby are avoided the so-called 'post-treatment paralyses' which occasionally follow certain other methods of treatment.

(3) *Accuracy of dosage.* That uniformly successful results have been established can be claimed for no method unless dosage of vaccine can be accurately determined.

In regard to cord methods two factors must be taken into account, which militate against an accurate estimation of the number of immunizing units injected into a patient.

(*a*) Cords differ much in size, varying largely in proportion to the size of rabbit employed. A very appreciable difference must exist between the numbers of immunizing units contained in 1 c.c. of thick and in 1 c.c. of thin cord, respectively.

(*b*) Where the dried cord method is used, it will be obvious that a ten days' dried cord, from a large rabbit, will contain, normally, more living virus than a ten days' cord from a small one because desiccation proceeds more rapidly in the latter. Such difficulties do not obtain with carbolized vaccine. If care be taken to pound the brain, during manufacture, for a fixed period, say twenty minutes, and to filter the resultant suspension through gauze of uniform thickness, emulsions of unvarying strength are produced.

(4) Its dosage over fourteen consecutive days (the complete period of treatment) remains constant for all bitten persons, irrespective of age, sex, severity of bite, location and multiplicity of wounding, interposition of clothing, and different conditions requiring consideration when other methods of treatment are employed.

The reason for the application of a universal dosage lies in the fact that each case for which treatment is prescribed is regarded as being sufficiently serious to warrant the full and intensive dosage given by this method.

(5) *Economy and rapidity of production.* The use of carbolized vaccine permits of great economy both in respect of animals and of time. From a rabbit of average weight (1,400 grammes) can be produced vaccine sufficient for twelve complete courses of treatment. Further, one does not require to inoculate rabbits daily, but only as occasion demands and just often enough to maintain the ' strain.'

The actual material cost of treatment of nearly 2,000 bitten persons, here, during the past two years, has been little more than the purchase price of 150 rabbits. The time taken to produce the vaccine is short and we have clearly shown that any well-equipped laboratory can, in addition to its routine work, undertake the successful manufacture of the vaccine without additional expert staff.

An illustration of the rapidity of production is afforded by a recent occurrence when, on a farm over 100 miles from the Central Institute, 75 valuable animals were bitten by a rabid dog.

The issue of a quantity of vaccine (5,250 c.c.) sufficient for the treatment of these 75 animals was made without delay, and within nine days our reserve stock was at its normal level.

(6) Carbolized vaccine retains its maximal potency and powers of immunization for a period of at least three months if preserved under requisite conditions—away from light and in an ice-box.

It is, consequently, suitable for use in small countries where rabies is present, but too rare to justify the expenditure involved in the creation of Anti-Rabic Institutes. Such countries can purchase, from time to time, quantities of vaccine sufficient for estimated maximal requirements and their stock can be renewed quarterly at small expense. Transjordania—a country adjoining and obtaining its vaccine supplies from Palestine—affords an excellent example.

On the other hand, when living virus is employed for treatment, vaccine cannot be sent to a distance without a diminution of efficacy and without risk of its becoming infected. It is for this reason that, in our belief, carbolized vaccine is the only one of practical value in the prophylactic and curative treatment of animals.

(7) The vaccine is manufactured in a Central Institute and can be issued therefrom to any number of treatment centres where its administration to bitten persons forms part of the routine duties of the Government medical officers there. The advantages to the bitten persons of this are as follows :—

(*a*) Treatment can be begun without loss of time—an incalculable advantage in a condition where the importance of the time factor is paramount.

(*b*) The patient can be treated at or near his own home, and thereby is avoided the necessity for his undertaking long fatiguing journeys.

(*c*) The bitten person may move from town to town in accordance with the dictates of his business and be assured of an uninterrupted course of treatment.

In this connection, and to demonstrate the exceptional applicability of this form of treatment to unexpected circumstances, we would refer to an episode which occurred during 1923. In a military camp at Sarafand, two British and five Indian soldiers were severely bitten by a jackal. The jackal was shot, its brain extracted and forwarded to the Central Institute, where the finding of Negri-bodies and a positive biological test proved the animal to have been rabid at the time of biting. The bitten persons were treated at Ramleh Anti-Rabic Centre for seven consecutive days, at the end of which time the Indian regiment was ordered to proceed abroad. The Regimental Medical Officer was supplied with vaccine sufficient for seven further injections to each patient, and the remaining half of the course was administered on board ship. Reports forwarded later showed that treatment had been successful in each case.

Probably one of the most satisfactory results of our procedure, however, is that no case of hydrophobia has occurred during the past year for lack of facilities for treatment. In marked contrast to this state of affairs were the conditions (summarised in Table I) obtaining in 1922—in the year previous to the adoption of the present system of decentralisation of treatment.

(8) *Efficacy.* A.—*Theoretical considerations.* It has to be admitted, however, that the only factor determining ideal treatment is its ' Efficacy.'

If a treatment is to be universally successful it has to be able not only to prevent the onset of hydrophobia in the case of average severity, but also to ward off the disease in grave cases of short incubation periods.

The greatest advantage claimed for carbolized vaccine and its

period of administration is that it is an attempt to deal with such cases as may have short incubation periods. There can be no possibility of cure once the virus has reached the brain ; now, in a certain percentage of cases the virus does actually attach itself to the brain in or in about fifteen days ; it is obvious, therefore, that any treatment calculated to prevent the disease in these cases must aim not only at producing in the system a sufficiency of antibodies, but at producing them *within fifteen days*. Under such circumstances the time limit is of first importance, and the logic of ' intensifying ' treatments of head and face bites by prolonging them beyond the minimal period sufficient to excite and promote antibody formation in as great an area as possible is by no means clear. Surely here the thing to do is to increase the dosage administered within the minimum period of time at one's disposal. The importance of realising this cannot be over-estimated, and a glance at this modified table of Bauer (II) will show short incubation periods to be by no means rare. Further, in Table I, are two such cases.

Table II (after Bauer).

Number of days incubation	Percentage of total
1–19	8·24
20–39	28·34

A short intensive course of treatment might likewise prove of extreme value in those cases where bitten persons report at an institute late. Here again time is all-important and the maximum dosage bearable should be administered in the shortest possible period.

Moreover, the use of brain matter instead of cord doubtless contributes towards the efficacy of carbolized vaccine and its superiority over cord methods.

Brain matter is said by Nitsch to be ten times more virulent

than spinal cord. In using brain, therefore, we are giving a larger proportion of specific antibody-producing substance and a smaller one of the useless, probably harmful, nervous tissue than is practised in methods of cord immunization.

B.—*Practical results*. We shall first record the experimental and then the practical evidence on which our assertions as to the efficacy of this method are based.

(1) *Experimental.*

The subjoining Tables III and IV are self-explanatory.

Table III

Immunizing Experiments.

No. of experiment	Animal	Duration of Treatment	Quantity of 1% carbolized vaccine injected subcutaneously	Test	Result
1	Rabbit	14 days	28 c.c.	0·2 c.c. of 1% fixed virus emulsion introduced subdurally 15 days after last injection.	Lived
2	Rabbit	14 days	28 c.c.		Lived
3	Rabbit	14 days	28 c.c.		Died in 15 days
4	Rabbit	14 days	28 c.c.		Lived.
5	Rabbit	14 days	28 c.c.		Died in 18 days
6	Rabbit	Not treated	None		Died in 8 days
7	Rabbit	Not treated	None		Died in 8 days
8	Rabbit	Not treated	None		Died on 9th day

The temporary nature of the immunity conferred is well illustrated in regard to rabbit No. 2. Without prior immunization this animal was innoculated with 0.2 c.c of 1 per cent. emulsion of fixed virus, fourteen months later, and died in eight days.

To show the evidence of immunity in the serum of rabbits treated with 1 per cent. carbolized vaccine, we have, guided by examples from existing literature, performed the experiments recorded in the next table.

Table IV.

Animal immunized	Vaccine used for immunizing	Time after completion of treatment when serum was tested	Proportion of serum and 1% fixed virus emulsion tested	Tests applied to mixture of serum and virus	Result
Rabbit	1% carbolized anti-rabic	15 days	Serum 1 c.c. + fixed virus 1 c.c. incubated 2 hours at 37°	Subdurally into rabbit	Remained well
Rabbit	do.	do.	do.	do.	do.
Rabbit	do.	do.	do.	do.	Died 12th day
Rabbit	do.	do.	Only fixed virus 1% emulsion	do.	Died after 8th day
Rabbit	do.	do.	do.	do.	do.
Rabbit	Not immunized	Directly	do.	do.	Died in 8 days
Rabbit	do.	do .	do.	do.	do.

(2) *Deductions from treatment of bitten persons.*

In the various records given below it has been considered advisable to include in the first part of each table, mostly for purposes of interest and comparison, the total number of bitten persons attending the various anti-rabic treatment centres ; the number whose treatment was considered to have been unnecessary as reckoned by the biting animals having remained alive and well after ten days' observation, and the number of cases where a regular and complete course of treatment was carried out. On the last number alone have the death and so-called ' failure ' rates been estimated.

The only fair and accurate means, however, of arriving at the actual success or failure of any line of treatment is to base the final calculations only on the number of bitten persons treated who had been definitely or presumably exposed to risk of infection.

The second part of each table, therefore, consists of an enumeration of :

(1) Those persons definitely-at-risk as proved by :—

(*a*) Laboratory investigation.

(*b*) Veterinary officer's certificate obtained after observation of the biting animal.

(2) Those persons presumably-at-risk, i.e., who had been bitten by animals fulfilling the conditions laid down under A. General Considerations, paragraph 1, items (*d*) and (*e*).

(3) Death and ' failure ' rates calculated on a total of (1) + (2).

Statistics from May 1, 1923, to April 30, 1925.

Part 1.

Number of persons treated at various Government anti-rabic treatment centres in Palestine	1,920
Number of treatments interrupted or unnecessary	470
Number of regular and complete treatments administered ...	1,450
Total Deaths	12
Death rate	0·82%
Deaths occurring later than 15 days after completion of Treatment	4
'Failure' rate	0·27%

Part 2.

Number of persons definitely-at-risk—	
(*a*) Proved by laboratory investigation	270
(*b*) Proved by veterinary officers' certificates	123
Number of persons presumably-at-risk	420
Death rate	1·47%
'Failure' rate	0·49%

The above statistics, however, represent the results obtained from the combination of two definite work periods differentiated by alteration in daily dosage; thus, whereas in the period 1923-24, treatment consisted of the daily administration of 2 c.c. carbolized vaccine over fourteen consecutive days, during 1924-25 a dosage of 5 c.c. daily over the same number of days was substituted.

The results achieved during the two periods afford interesting comparison.

Part 1.	Period 1923-24 Dosage 2 c.c. of 1% emulsion	Period 1924-25 Dosage 5 c.c. of 1% emulsion
Number of persons treated	886	1,034
Unnecessary treatments	138	332
Regular and complete treatments	748	702
Total deaths	9	3
Death rate	1·2%	0·4%
'Failures'	4	0
'Failure' rate	0·5%	0
Part 2.		
Number of persons definitely-at-risk—		
(*a*) Proved by laboratory investigation	180	80
(*b*) Proved by veterinary officers' certificates	48	75
Number of persons presumably-at-risk ...	213	207
Death rate	2%	0·8%
'Failure' rate	0·9%	0

It will be observed that 307 and 340 persons belonging respectively to the 1923-24 and 1924-25 periods are not included in Part II, although they have been bitten by animals fulfilling the conditions laid down in A. General Considerations, paragraph 1, items (*a*), (*b*) and (*c*)—conditions which demand the immediate treatment of the bitten persons from the point of view that the biting animals are to be considered rabid. Such number, if included, would obviously lessen both the death and 'failure' rate, thereby elevating the degree of efficacy of this form of treatment.

It is generally admitted that a certain percentage of cases cannot be benefited by any form of anti-rabic treatment. In such cases the incubation period is very short and the virus reaches the brain before a sufficient degree of immunity can be conferred. Excellent examples are afforded by numbers 2, 4, and 6, in Table I, and by the first line statistics of Table II.

On the other hand it must be admitted that when a patient dies of hydrophobia, say one, two, or three months after completing a full and regular course of treatment, this case cannot be included in the above category but must be considered as a failure of treatment in that either the effect of treatment was nil or that it sufficed merely to delay the arrival of the virus in the brain, thereby prolonging the incubation period of the disease, which latter alternative is exemplified in Table III, number 3 and 5, of our immunizing experiments.

Now in view of the results obtained in the 1923-24 period, with the administration of 2 c.c. daily for fourteen days, it may be a matter for surprise that we resolved to make an alteration in dosage to 5 c.c. daily over a similar period.

However, a study of the following four cases—our only failures of treatment as judged by the conventional standards, viz., when hydrophobia supervenes later than fifteen days after completion of a regular course of treatment—was mainly instrumental in bringing about our decision.

Case 1. Male, aged 10 years, severely bitten on forehead, hand and leg through naked skin by a jackal, reported one day after bite for treatment, the wound not having been cauterized before arrival. Treatment was regular over 14 days. Symptoms developed 59 days after the date of bite, and 44 days after completion of treatment.

Case 2. Male, aged 35 years, severely bitten on face, eyelid, and thumb by jackal through naked skin, reported three days after bite, the wound not having been cauterized, and attended regularly for treatment. Symptoms appeared 81 days after the bite and 65 days after completion of treatment.

Case 3. Male, aged 8 years, bitten slightly on upper extremity through naked skin by a dog, arrived two days after bite with wound not cauterized. Symptoms occurred 36 days after the bite and 21 days after completion of treatment.

Case 4. Male, aged 30 years, bitten severely through clothing on lower extremity by a dog, arrived immediately after for treatment and had wound cauterized with fuming nitric acid. Treatment was administered regularly over 14 days. Hydrophobia supervened 39 days after the bite and 26 days after completion of treatment.

We felt convinced that these four cases died, not as the result of any special exaltation of a virus (virus de rue renforcé) or shortness of incubation period, but because the treatment administered had not been sufficiently intensive : with this conclusion Professor Fermi, of Sassari, to whom we submitted the facts, was in complete agreement. (It is, however, worthy of record that thirteen other persons, bitten by the animals inflicting bites on the four persons cited, received full and regular courses of vaccine also, and all thirteen are to-day alive and well, one-and-a-half years after completion of treatment.)

As a result an alteration in dosage was effected for all cases, on May 1st, 1924, after a month's preliminary trial had demonstrated beyond question the ability of children and adults alike to tolerate the daily increase from 2 to 5 c.c.

It was resolved by us to make an increase in daily dosage rather than in the period of vaccine administration, so that the method of treatment might be made as widely applicable as possible and especially with regard to such cases as might have short incubation periods.

Although we consider that results in human beings have justified the alteration, yet Table V will demonstrate our inability to adduce experimental proof of the value of increased dosage in laboratory animals.

Further, from this table it would appear that :—

(*a*) Better results in rabbits are obtained by the giving of small doses over a number of days (14) than of larger doses over a shorter period.

(*b*) It is impossible to reduce below a certain limit the time over which the total quantity of vaccine, ordinarily sufficient for complete immunization, can be usefully administered.

(*c*) As large a dose as 30 c.c. of a 0.5 per cent. emulsion in 0.25 per cent. carbolic may be given without the production of toxic symptoms.

Table V

Experimental animal used	Dose and Period for Immunization					Whether or not animal survived treatment	Subdural Test
	2 c.c. daily for 14 days	4 c.c. daily for 14 days	6 c.c. daily for 10 days	15 c.c. daily for 3 days	One injection of 30 c.c.		2 weeks after treatment tested with 0·2 c.c. of 1% emulsion of fixed virus
Rabbit	1	...	...	...	...	Survived	Survived
Rabbit	1	...	...	...	...	Survived	Died
Rabbit	1	...	...	...	...	Survived	Died
Rabbit	1	...	...	...	...	Survived	Survived
Rabbit	...	1	...	...	...	Survived	Survived
Rabbit	...	1	...	...	...	Survived	Died
Rabbit	...	1	...	...	...	Died	...
Rabbit	...	1	...	...	...	Survived	Died
Rabbit	...	...	1	...	...	Survived	Survived
Rabbit	...	...	1	...	...	Survived	Died
Rabbit	...	...	1	...	...	Survived	Died
Rabbit	...	...	1	...	...	Survived	Died
Rabbit	...	...	...	1	...	Survived	Died
Rabbit	...	...	...	1	...	Survived	Died
Rabbit	...	...	...	1	...	Survived	Died
Rabbit	...	...	...	1	...	Survived	Died
Rabbit	...	...	...	...	1	Survived	Died
Rabbit	...	...	...	...	1	Survived	Died
Rabbit	...	...	...	...	1	Died	...
Rabbit	...	...	...	...	1	Survived	Died

We would now draw attention to the fact that in the records of statistics published above have been included figures for total deaths and for the so-called failures of treatment as well as their respective percentages.

'Failure,' in accordance with convention, is applied only to

those cases which, in spite of treatment, develop hydrophobia later than fifteen days after a complete anti-rabic course has been administered. By the same convention are excluded from ' failures ' all bitten persons dying during treatment or within fifteen days of its completion.

(Remlinger, e.g., has shown that during 1901-1908, in Constantinople, where the original Pasteur method is utilised, of persons dying despite treatment no fewer than 80 per cent. could be so excluded.)

Statistics based on this mode of computation will obviously vary with regard to :—

(*a*) Length of time taken to adminster a course of treatment.

(*b*) Lateness of arrival of the bitten person for treatment.

The longer a person defers reporting for treatment, and the longer the period of treatment—the lower the ' failure rate ' of an institute.

It is felt that such statistics tend unduly to emphasise the value of certain forms of anti-rabic treatment and especially of such as normally require a lengthy period for adminstration.

We realise that this method of recording deaths and failures would be ideal, if all institutes were to employ the same method whereby the same dosage of a similarly prepared vaccine was administered during the same period of time. As matters stand at present, however, when anti-rabic methods are many and diverse, it is our opinion that the only way to present statistics which can admit of real comparison is a simple enumeration of the deaths occurring at an institute and the percentage such bears to the total attending population proved or believed to be at-risk.

Deaths from hydrophobia should then be reported on in full, with especial reference to the duration of treatment, to the number of days intervening between completion of treatment and onset of symptoms, to the lateness of arrival for treatment, and to the irregularity of attendances during the course.

This information, in addition to that supplied in Appendix I, will generally enable an impartial pronouncement to be made upon such cases in their relation to treatment.

G.—Records. It was at once recognised that one of the criticisms most likely to be levelled against decentralisation of treatment would be the presumed unreliability of the records of available information.

With the view, therefore, of meeting just such a charge we evolved the present procedure of keeping records of the particulars of all patients treated in the various Government Centres.

Appendix I gives the form which enables a complete register of cases undergoing anti-rabic treatment to be kept at each treatment centre by the medical officer in charge. Immediately a patient has completed his course, the original form is submitted to the office of the Central Institute for filing, while the duplicate is retained at the treatment centre concerned. Three months after the last day of completion of treatment, a final report on the patient is submitted to the Central Institute by the responsible medical officer and this report certifies to the patient being in good health (or otherwise) on that date. This procedure, we consider, allows of the ready compilation of exact statistics.

IV. SUMMARY

1. Carbolized Anti-rabic Vaccine is an efficient and safe treatment for persons bitten by rabid animals.

2. It can be manufactured without additional staff in any well-equipped laboratory.

3. It can be distributed to any number of treatment centres where as good results attend its use as at the place of its production.

4. Better results have followed the employment here of a dosage of 5 c.c. daily of a 1 per cent. emulsion, over fourteen days, than of 2 c.c. of the same emulsion over the same period.

5. Carbolized vaccine is most practicable in the curative and prophylactic treatment of farm animals.

It can be easily administered in rural districts by veterinary officers.

6. It is a great advance on older methods of treatment in the wideness of applicability and economy of production of the vaccine. It is at once the most economical and utilitarian mode of treatment.

7. Bitten persons can be treated at or near their own homes, and thus—the all-important consideration of immediate treatment aside—they are spared the expenses connected with travel to, and residence in, a strange town.

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Our thanks are due to the Director of Health, Col. G. W. Heron, D.S.O., O.B.E., for his unfailing encouragement and for his affording us facilities which rendered the whole scheme of decentralisation possible. We are indebted also to Dr. Miftah, Director of the Pasteur Institute, Cairo, for many favours, but especially for his ungrudging assistance in the training of our personnel.

For the sake of completeness, we have considered it advisable to add three appendices :—

I. The form employed to register cases undergoing anti-rabic treatment.

II. Regulations for the control of rabies (in which is incorporated the procedure to be adopted in the case of the bitten animal). These regulations made under Art. 43 of the Ottoman Law concerning Diseases of Animals, and drawn up by Col. E. R. Sawer, Director of Agriculture, have been in force since December, 1924.

III. Further measures adopted to free Palestine from rabies and hydrophobia.

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APPENDIX I

Local Form O. M. 186

Department of Health

REGISTER OF CASES UNDERGOING ANTI-RABIC TREATMENT.

No. Date District

Information about patient :

Name Age Profession
Residence and Address
Nationality Sent by
Date of bite Animal inflicting bite
Station where bitten

Wounds

	Number	Gravity	Bitten on naked skin or through Clothing
Head and neck			
Upper extremity			
Lower extremity			
Body			

Have wounds been previously treated ? (cauterized) and when ?

Information about the animal.

Owner of animal Address
What has become of the animal ?
Other persons bitten, with names and addresses
Other information (e.g. " dog bit unprovoked ")

Diagnosis.

1. Condition of animal from enquiry
2. Microscopical Researches (Negri bodies)
3. Experimental inoculation ? Result Date

Treatment.

1. When started 2. Vaccine and Dosage 3. Serial No. of Vaccine

4. Attendances

Month															
Dates															

5. Conduct of patient during treatment
6. Accidents, if any, during treatment
7. Other remarks

Signature of M. O.

Final Report on Patient.

No.
On being three months after the last day of the completion of treatment, the patient is alive in good health (or otherwise) and is living at (address)
District Signature of M. O.
Date

APPENDIX II

REGULATIONS FOR THE CONTROL OF RABIES.

1. Every person having had in his possession or under his charge an animal affected with or suspected of Rabies shall give notice of the fact with all practicable speed to the Mukhtar, President of the Municipality or Police as the case may be. Failure to give such notice renders the person liable to a fine of £1 to £5 or to imprisonment not exceeding one month.

2. It is the duty of Mukhtars, Presidents of Municipalities and Police, on receiving such notice, to destroy the affected animal or to place it in strict isolation, and to transmit the information immediately to the District Governor or District Officer who will delegate the Veterinary Inspector to institute inquiries.

3. On confirmation of the disease and receipt of the report of the Veterinary Inspector, the District Governor or District Officer shall form a sanitary commission in accordance with the provisions of the said Ottoman Law, to execute the measures necessary for the control and suppression of the disease.

The commission shall be composed of the District Officer as president, and the Veterinary Officer, a representative of the Public Health Department, the Local Commandant of Police, and a member of the Municipal Council as members.

4. Every animal affected with Rabies shall be destroyed. Any animal whose behaviour leaves no doubt as to its being rabid shall be destroyed on the spot, and its body, in the case of dogs, cats and small animals, taken to the nearest District Veterinary Officer for disposal.

5. Animals bitten by rabid animals shall be dealt with as follows :—

(*a*) Donkeys, dogs, cats, monkeys, etc., shall be destroyed.

(*b*) Local camels ; bulls, cows, calves, oxen, sheep and goats shall be slaughtered ; but provided such animals are slaughtered within seven days of the date when first bitten, their carcases, if free from other diseases, may be exposed for sale as food.

(*c*) Valuable horses, mules, bulls, cows and calves shall be destroyed, or (1) strictly isolated for four months under the observation of Government Veterinary Officers and on premises approved by the Department of Agriculture, and (2) vaccinated with Anti-rabic Vaccine at the owner's risk and cost.

It is prohibited to sell such animals for any purposes whatsoever, during the period of observation.

6. Every animal bitten by a suspectedly rabid animal, and any dog which has been in contact with a suspectedly rabid dog shall either be destroyed or shall be strictly isolated :—

(*a*) Under the observation of Government Veterinary Officers, and

(*b*) In special cages, kennels, or stables, or on premises approved by the Department of Agriculture ; and

(*c*) At the entire risk and expense of the owner ; and

(*d*) For a period of six months in the case of dogs, or four months in the case of herbivorous animals or in both cases for such a period as will allow the diagnosis to be confirmed by the District Veterinary Inspector.

7. Every animal which has bitten a human being shall be placed in strict isolation and under observation for a period of at least ten days at the owner's risk and expense.

8. In no case may such animals be detained for purposes of observation by any private person or institution.

9. Animals will be destroyed by order of the District Officer or the District Veterinary Inspector, and no compensation will be paid in respect of such animals when they are :—

(*a*) Rabid or suspectedly rabid, or bitten by such animals ;

(*b*) In contact with a rabid or suspectedly rabid dog or other carnivorous animals.

10. The carcases of rabid or suspectedly rabid animals will be burned or deeply buried unskinned, but only after the examination by a District Veterinary Inspector or on the authority of the District Officer, in places selected by them.

11. The District Governor or President of a Sanitary Commission formed under the Law, shall in any locality where a case of rabies has occurred, issue a notice proclaiming the measures to be taken to control and suppress the disease, and the owners or persons in charge of animals shall observe and comply with such regulations.

12. The Administrative Authority, after notifying the public in the town or area, may proceed at any time to poison or destroy in any manner vagrant, stray, ownerless or collarless dogs and dogs not carrying the municipal tally.

13. Any person who fails to comply with any of the foregoing regulations or orders issued by the District Governor or Sanitary Commission for the Suppression of Rabies, or who does not assist in execution of such orders, shall be liable to prosecution before a magistrate under Art. 39 of the Ottoman Diseases of Animals Law of the 5th December, 1910 (1329 Moslem year), and on conviction to imprisonment not exceeding three months or to a fine not exceeding £20.

APPENDIX III

Apart from the preparation of a suitable vaccine for the treatment of persons bitten by rabid animals further measures were adopted to deal with the menace.

(*a*) The extermination of jackals and stray dogs—the common transmitters of the disease to human beings ;

(*b*) The education of the public in town, district and village regarding the nature of the disease, its method of transmission and the action to be taken by an individual who has been exposed to risk of infection from being bitten by a dog or other animal.

In regard to (*a*), the following action was taken by the Departments of Agriculture, Police and Prisons, and Health acting together :—

(1) The organisation of a constant campaign conducted by the Gendarmerie in country districts to lay bait poisoned with strychnine capsules in places frequented by jackals and pariah dogs. The campaign is carried out

along lines carefully worked out by the Department of Agriculture and during the present year has resulted in the finding of over 1,000 dogs and 750 jackals. The number of animals killed is known to exceed those actually found dead, as many which have swallowed poisoned baits travel some distance before the poison takes effect ;

(2) In town areas the first step towards reducing the numbers of ownerless and pariah dogs was to regulate the registration and licensing of dogs kept by householders as guards or domestic pets. This registration is effected by the staff of the Municipalities under model regulations drafted by the government Departments concerned and adopted by all towns. Municipal employees are authorised to apprehend and destroy all dogs found at large not bearing on their collars a numbered tally indicating that they have been duly licensed.

When the number of ownerless dogs is found to be increasing in any given area of a town in spite of these measures, the assistance of the Police is called upon and the animals are destroyed by shooting.

From 1st January, 1923, until 30th June, 1925, over 20,000 ownerless dogs were destroyed.

Municipalities furthermore are required to make arrangements for the safe custody of dogs whose observation by a veterinary officer is necessary on account of their suspicious behaviour or unwarranted attacks on human beings. This is effected by the Municipalities providing 'Observation Kennels' constructed in accordance with plans prepared by the Department of Health and approved by the Chief Veterinary Officer.

In regard to (*b*), articles have been written for publication in the newspapers of the country drawing attention to the dangers of hydrophobia and informing the pub'ic where to present themselves for anti-rabic treatment if they chance to have been bitten by a dog or other animal. Pamphlets have been written in all the official languages for distribution in schools. Through the medium of the Department of Education these pamphlets reach a very large number of homes throughout the country and opportunity is taken by the teachers when giving these papers to the children to explain to them in short and simple language the essential facts concerning the disease and its prevention.

This educative work is of great value, for in hydrophobia no less than in other communicable disease the intelligent co-operation of the public is essential to secure the success of preventive measures undertaken by the Government.